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EXAMINER	
CALAMITA, HEATHER	
ART UNIT	PAPER NUMBER
1637	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/06/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/395,409	CANTOR ET AL.	
	Examiner	Art Unit	
	Heather G. Calamita, Ph.D.	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-49,51-54,58-60,63-76,86,88-124 and 127-147* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-49,51-54,58-60,63-76,86,88-124 and 127-147* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/14/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

1. Claims 1-49, 51-54, 58-60, 63-76, 86, 88-124, 127-144 and newly added claims 145-149 are currently pending and under examination. All arguments have been fully considered and thoroughly reviewed, but are deemed not persuasive for the reasons that follow. Any objections and rejections not reiterated below are hereby withdrawn.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-17, 19-27, 29-33, 35-37, 43-49, 51-52, 54, 64-70, 73-76, 124 and 127 are rejected under 35 U.S.C. 103(a) as being unpatentable over Köster (WO 94/16101 07/21/1994) in view of Cantor (USPN 5,503,980, 04/02/1996).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the

inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Köster teaches a method for sequencing a target nucleic acid, comprising the steps of: (see whole document, especially p. 11 lines 27-30)

fragmenting the target nucleic acid molecule to produce a set of nucleic acid fragments each containing a sequence that corresponds to a sequence of the target nucleic acid (see p. 13 lines 9-24 and Fig 1, where the target nucleic acid is fragmented by enzymatic digestion);

hybridizing the set to an array of nucleic acid probes to form a target array of nucleic acid molecules, wherein each probe comprises a single-stranded portion such that each member of the set hybridizes to a member of the array of probes (see p. 14 lines 31-33) and:

the array comprises a collection of probes with sufficient sequence diversity in the variable regions to hybridize all of the target sequence with complete or nearly complete discrimination (see

determining molecular weights of nucleic acids in the target array to identify hybridized probes; and based upon the hybridized probes, determining the sequence of the target nucleic acid (see p. 15 lines 2-4).

With regard to claim 2, Köster teaches the molecular weights are determined by chromatography (see p. 8 lines 14-16).

With regard to claim 3, Köster teaches the molecular weights are determined by mass spectrometry (see p. 11 lines 27-30).

With regard to claim 4, Köster teaches the mass spectrometry comprises a step selected from the group consisting of laser heating, droplet release, electrical release, photochemical release, fast atom

bombardment, plasma desorption, matrix-assisted laser desorption/ionization, electrospray, and resonance ionization, or a combination thereof (see p. 11 lines 27-30).

With regard to claim 5, Köster teaches the mass spectrometry comprises a step selected from the group consisting of Fourier Transform, ion cyclotron resonance, time of flight analysis with reflection, time of flight analysis without reflection, and quadrupole analysis, or a combination thereof (see p. 6 lines 31-33, p. 17 lines 2-5).

With regard to claim 6, Köster teaches the mass spectrometry comprises matrix-assisted desorption ionization and time of flight analysis (see p. 17 lines 2-5).

With regard to claim 7, Köster teaches the mass spectrometry comprises electrospray ionization and quadrupole analysis (see p. 16 lines 31-33).

With regard to claim 8, Köster teaches two or more molecular weights are determined simultaneously (see p. 12 lines 1-3).

With regard to claim 9, Köster teaches the step of enzymatically extending the nucleic acid probes of the target array using the hybridized target nucleic acid as a template to form extended strands prior to the step of determining the molecular weights of the nucleic acids (see p. 15 lines 37-39, p. 16 line 1).

With regard to claims 10, 51, 52 and 76, Köster teaches the extended strands comprise DNA, RNA, PNA or combinations thereof (see p. 14 lines 35-37).

With regard to claims 11 and 48, Köster teaches the step of extending is performed in the presence of chain elongating nucleotides and chain terminating nucleotides (see p. 12 lines 24-29).

With regard to claim 12, Köster teaches the array comprises nucleic acid probes having at least one mass-modifying functionality (see p. 15 lines 9-12).

With regard to claim 13 and 14, Köster teaches the mass-modifying functionality is coupled to a heterocyclic base, a sugar moiety or a phosphate group (see p. 15 lines 9-12).

With regard to claim 15, Köster teaches the mass-modifying functionality is coupled to a purine at position C2, N3, N7, or C8 (see Fig 7A).

With regard to claim 16, Köster teaches the mass-modifying functionality is coupled to a deazapurine at position N7 or N9 (see Fig 8 A & B).

With regard to claim 17, Köster teaches the mass-modifying functionality is coupled to a pyrimidine at position C5 or C6 (see Figs 7A & B). With regard to claim 18, Köster teaches the mass-modifying functionality is selected from the group consisting of F, CI, Br, I, SiR_3, $Si(CH_3)_3$, $Si(CH_3)_2(C_2H_5)$, $Si(CH_3)(C_2H_5)_3$, $(CH_2)_nCH_3$, $(CH_2)_nNR_2$, CH_2CONR_2, $(CH_2)_nOH$, CH_2F, CHF_2, and CF_3; wherein n is an integer; and wherein R is selected from the group consisting of -H, deuterium and alkyls, alkoxys and aryls of 1-6 carbon atoms, polyoxymethylene, monoalkylaled polyoxymethylene, polyethylene imine, polyamide, polyester, alkylated silyl, heterooligo/polyaminoacid and polyethylene glycol (see Figs 9 and 10).

With regard to claim 19, Köster teaches the mass-modifying functionality is -Na or -XR, wherein X is selected from the group consisting of -0-, -NH-, -NR-, -S-, $-OCO(CH_2)_nCOO-$, $-NHCO(CH_2)_nCOO-$, $-OSO_2O-$, $-OCO(CH_2)_n-$, -NHC(O)-, and -C(O)NH-, and n is an integer from 1 to 20; and wherein R is selected from the group consisting of -H, deuterium and alkyls, alkoxys and aryls of 1-6 carbon atoms, polyoxymethylene, monoalkylated polyoxymethylene, polyethylene imine, polyamide, polyester, alkylated silyl, heterooligo/polyaminoacid and polyethylene glycol (see Figs 9 & 10).

With regard to claims 20-26, Köster teaches X is –NHC(S)-, -NHC(S)NH-, $-NC_4O_2H_3S-$, $-OCO(CH_2)_nS-$, $-OCO(CH_2)S-$, X is -OP(O-alkyl)-, -OPO(O-alkyl)- (see Figs 9 & 10).

With regard to claim 27, Köster teaches the mass-modifying functionality is a thiol moiety (see p. 15 lines 7-10).

With regard to claim 29, Köster teaches the mass-modifying functionality is an alkyl moiety (see p. 15 lines 7-10).

With regard to claim 30, Köster teaches the alkyl moiety is generated by using iodoacetamide (see p. 15 lines 7-10).

With regard to claim 31, Köster teaches the step of removing alkali cations (see p. 15 lines 24-27).

With regard to claims 32 and 33, Köster teaches the alkali cations are removed by ion exchange (see p. 15 lines 28-29).

With regard to claims 35-37, Köster teaches the target nucleic acid is provided from a biological sample, and that sample is obtained from a patient, or is provided from a recombinant source (see p. 13 lines 9-24).

With regard to claims 43-47, Köster teaches the fragments are provided by enzymatic digestion of the target nucleic acid, the enzymatic digestion is carried out by a nuclease; the nucleic acid fragments are provided by physically cleaving the target nucleic acid the nucleic acid fragments are provided by enzymatic polymerization, wherein the target nucleic acid is a template the enzymatic polymerization is a nucleic acid amplification process selected from the group consisting of strand displacement amplification, ligase chain reaction, Qβ replicase amplification, 3SR amplification, and polymerase chain reaction (see p. 13 lines 9-24 and Fig 1).

With regard to claim 49, Köster teaches the nucleic acid fragments are provided by synthesizing a complementary copy of the target sequence (see p. 13 lines 18-21).

With regard to claim 54, Köster teaches the probes are single-stranded (see p. 12 lines 32-34).

With regard to claims 64, Köster teaches the array of nucleic acid probes is attached to a solid support (see p. 16 lines 13-24).

With regard to claims 65, Köster teaches the solid support is selected from the group consisting of plates, beads, microbeads, whiskers, combs, hybridization chips, membranes, single crystals, ceramics, and self-assembling monolayers (see p. 16 lines 13-16).

With regard to claim 66, Köster teaches the probes are conjugated with biotin or a biotin derivative and wherein the solid support is conjugated with avidin, streptavidin or a derivative thereof (see p. 15 line 17).

With regard to claim 67, Köster teaches each probe is attached to the solid support by a bond selected from the group consisting of a covalent bond, an electrostatic bond, a hydrogen bond, a cleavable bond, a pholocleavable bond, a disulfide bond, a peptide bond, a diester bond, a selectively releasable bond and combinations thereof (see p. 15 lines 14-24).

With regard to claim 68, Köster teaches the cleavable bond is cleaved by a cleaving agent selected from the group consisting of heat, an enzyme, a chemical agent, and electromagnetic radiation, or a combination thereof (see p. 15 lines 20-24).

With regard to claim 69, Köster teaches the chemical agent is selected from the group consisting of reducing agents, oxidizing agents, and hydrolyzing agents, or a combination thereof (see p. 15 lines 16-17).

With regard to claim 70, Köster teaches the electromagnetic radiation is selected from the group consisting of visible radiation, ultraviolet radiation, and infrared radiation (see p. 14 lines 12-15).

With regard to claim 73, Köster teaches a spacer between each probe and the solid support (see Fig 23).

With regard to claim 74, Köster teaches the spacer is selected from the group consisting of oligopeptides, oligonucleotides, oligopolyamides, oligoethyleneglycerol, oligoacrylamides, and alkyl chains of between about 6 to about 20 carbon atoms, or combinations thereof (see p. 14 lines 31-33).

With regard to claim 75, Köster teaches the solid support comprises a matrix chemical that facilitates volatilization of nucleic acids for molecular weight determination (see p. 16 line 31).

With regard to claim 127, Köster teaches a system, comprising: a mass spectrometer; a computer; (see p. 11 lines 28-30, and p. 20 lines 33-38).

With regard to claims 146 and 147, Köster teaches the matrix chemical is 3-hydroxypicolinic acid, sinapinic acid or dihydroxybenzoic acid (see p. 38 lines 24-25).

Köster does not teach the probe comprises a single-stranded variable region.

Köster does not teach an array. Köster does not teach the array comprises a collection of probes with sufficient sequence diversity in the variable regions to hybridize all of the target sequence with complete or nearly complete discrimination.

Cantor teaches an array and a probe with a single stranded variable region and the array comprises a collection of probes with sufficient sequence diversity in the variable regions to hybridize all of the target sequence with complete or nearly complete discrimination (see col. 12 lines 6-17).

One of ordinary skill in the art at the time the invention was made would have been motivated to apply the method of probes with sequence diversity in the variable regions to hybridize all of the target sequence with nearly complete discrimination as taught by Cantor with the method for sequencing nucleic acid by mass spectrometry as taught by Köster in order to improve the analysis of the nucleic acids sequences. Cantor states, "Only the overhangs vary, and in principle an array of 4^n probes is needed to represent all 4^n possible overhangs of length n. The advantage of such an array is that it provides enhanced sequence stringency in detecting the 5' terminal nucleotide of the target DNA because of base stacking between the preformed DNA duplex and the newly formed duplex (see col. 12 lines 10-16). It would have been prima facie obvious to apply the method of generating probes with sequence diversity in the variable regions to hybridize all of the target sequence with nearly complete discrimination as taught by Cantor with the method for sequencing nucleic acid by mass spectrometry as taught by Köster to achieve the expected advantage of enhanced sequence stringency in detecting the 5' terminal nucleotide of the target DNA and therefore enable more accurate sequencing of the target DNA.

3. Claim 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over Köster (WO 94/16101 07/21/1994) in view of Cantor (USPN 5,503,980, 04/02/1996) and in further view of Weiss (USPN 6,025,193 02/15/2000).

The teachings and suggestions of Köster and Cantor are described previously.

Köster and Cantor do not teach or suggest the generation of a thiol moiety by using Beucage reagent.

Weiss teaches the generation of a thiol moiety by using Beucage reagent (see col. 19 lines 10-26).

One of ordinary skill in the art at the time the invention was made would have been motivated to apply the method of generating a thiol moiety as taught by Weiss with the method for sequencing nucleic acid by mass spectrometry as taught by Köster in order to improve the analysis of the nucleic acids sequences. Weiss states, "By using the sulfurization reagent, each and every "O" group of the phosphodiester bond can be substituted with a sulfur group" (see col. 19 lines 19-21). It would have been prima facie obvious to apply the method of generating a thiol moiety as taught by Weiss with the method for sequencing nucleic acid by mass spectrometry as taught by Köster to achieve the expected advantage of detecting a sulfurization reagent by which each and every "O" group of the phosphodiester bond can be substituted with a sulfur group.

4. Claims 34, is rejected under 35 U.S.C. 103(a) as being as being unpatentable over Köster (WO 94/16101 07/21/1994) in view of Cantor (USPN 5,503,980 04/02/1996).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter

of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(l)(1) and § 706.02(l)(2).

The teachings of Köster are described previously.

Köster does not teach ligating the hybridized target nucleic acids to the probes.

Cantor teaches ligating the hybridized target nucleic acids to the probes (see col. 8 lines 1-7).

One of ordinary skill in the art at the time the invention was made would have been motivated to apply the ligation of the probe to the target nucleic acid as taught by Cantor with the method for sequencing nucleic acid by mass spectrometry as taught by Köster in order to improve the fidelity of hybridization. Cantor states, "Ligation of the target nucleic acid to the complementary probe increases fidelity of the hybridization" (col. 8 lines 7-9). It would have been prima facie obvious to apply the ligation of the probe to the target nucleic acid as taught by Cantor with the method for sequencing nucleic acid by mass spectrometry as taught by Köster to achieve the expected advantage of an improved sequencing method due to the increased fidelity of the hybridization.

5. Claims 71-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Köster (WO 94/16101 07/21/1994) in view of Cantor (USPN 5,503,980, 04/02/1996) and in further view of Sanghvi et al. (USPN 6,214,551 04/10/2001).

The teachings and suggestions of Köster and Cantor are described previously.

Köster and Cantor do not teach or suggest the selectively releasable bond is 4,4'-dimethoxytrityl or a derivative thereof including 3 or 4 [bis-(4-methoxyphenyl)]-methyl-benzoic acid.

Sanghvi et al. teach the selectively releasable bond is 4,4'-dimethoxytrityl or a derivative thereof (see example 81, col. 58 lines 3-32). Although Sanghvi et al. do not teach the derivative 3 or 4 [bis-(4-methoxyphenyl)]-methyl-benzoic acid in particular, Sanghvi et al. disclose equivalent compounds and derivatives used for the same purpose (Example 81).

One of ordinary skill in the art at the time the invention was made would have been motivated to apply the selectively releasable bond of 4,4'-dimethoxytrityl or a derivative thereof as taught by Sanghvi with the method for sequencing nucleic acid by mass spectrometry as taught by Köster and Cantor in order to have a selectively releasable bond. Sanghvi et al. state, "This invention is also directed to methods for the selective binding of RNA for research and diagnostic purposes. Such selective, strong binding is accomplished by interacting such RNA or DNA with compositions of the invention which are resistant to degradative nucleases and which hybridize more strongly and with greater fidelity than known oligonucleotides or oligonucleotide analogs" (col. 31 lines 19-25). It would have been prima facie obvious to apply Sanghvi's selectively releasable bond of 4,4'-dimethoxytrityl or a derivative thereof with Köster's method for sequencing nucleic acid by mass spectrometry to achieve the expected advantage of an invention directed to methods for the selective binding of RNA for research and diagnostic purposes where such selective, strong binding is accomplished by interacting RNA or DNA with compositions of the invention which are resistant to degradative nucleases and which hybridize with greater strength and fidelity than known oligonucleotides or oligonucleotide analogs.

6. Claims 38-39, 53, 58-60, 63, 86, 88, 89-124, 128-145 are rejected under 35 U.S.C. 103(a) as being as being unpatentable over Köster (WO 94/16101 07/21/1994) in view of Cantor (USPN 5,503,980 04/02/1996).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(l)(1) and § 706.02(l)(2).

The teachings of Köster are described previously.

Köster does not teach probes that comprise a double stranded portion and a single stranded portion. Köster does not teach the probes are about 10 to about 1,000 nucleotides in length. Köster does not teach the variable region is about 4-20 nucleotides in length. Köster does not teach the single stranded region is about 4-20 nucleotides in length. Köster does not teach the fragments of nucleic acids comprise greater than about 104 different members and each member is between about 10 to about 1,000 nucleotides in length. Köster does not teach the array comprises a collection of probes with sufficient sequence diversity in the variable regions to hybridize all of the target sequence with complete or nearly complete discrimination.

Cantor teaches probes with a double stranded portion and a single stranded portion, the probes are about 10 to about 1,000 nucleotides in length, the variable region is about 4-20 nucleotides in length, the

single stranded region is about 4-20 nucleotides in length (see whole document especially col. 3 lines 32-36, see col. 5 lines 53-59, col. 7 lines 65-67 and col. 8 lines 1-7). Cantor teaches the fragments of nucleic acids comprise greater than about 104 different members and each member is between about 10 to about 1,000 nucleotides in length and the array comprises a collection of probes with sufficient sequence diversity in the variable regions to hybridize all of the target sequence with complete or nearly complete discrimination (see col. 6 lines 1-6).

One of ordinary skill in the art at the time the invention was made would have been motivated to apply the probes as taught by Cantor with the method for sequencing nucleic acid by mass spectrometry as taught by Köster in order to improve nucleic acid sequencing. Cantor states, "This invention is directed to methods for sequencing nucleic acids by positional hybridization, to procedures combining these methods with more conventional sequencing techniques, to the creation of probes useful for nucleic acid sequencing by positional hybridization, to diagnostic aids useful for screening biological samples for nucleic acid variations, and to methods for using these diagnostic aids" (col. 1 lines 10-16). It would have been prima facie obvious to apply the probes as taught by Cantor with the method for sequencing nucleic acid by mass spectrometry as taught by Köster to achieve the expected advantage of an improved sequencing method conferring the advantage of accurate high throughput analysis.

Response to Arguments

7. Applicants' arguments filed June 13, 2006, have been fully considered but they are not persuasive.

With respect to the teachings of Köster and Cantor, Applicants argue Köster teaches a method of comaarison of the mass difference measured between the nested fragments with the known masses of each chain terminating nucleotide which allows the sequence of each fragment to be determined. This method is based upon the mass of the fragments, aligning the fragments and determining the sequences.

Applicants argue the instant claims do not rely on Sanger sequencing but rather in detecting hybridized probes based on their molecular weights. This argument is not persuasive because Applicants use the open language of comprising so it is permissible for Köster to teach an additional element in the method, specifically, Sanger sequencing. Additionally, Köster is not relied on for the teaching of probe hybridization, Köster is relied on for the extensive teachings with respect to using mass labels for sequencing. Cantor is relied on for the teaching of probe hybridization. Additionally, Applicants argue Cantor do not teach detecting hybrids based upon molecular weight. This argument is not persuasive because Cantor is not relied on for teaching the use of mass labels for detection but rather Köster is relied on for this teaching. Applicant is reminded that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

With respect to the 103 (a) rejection of claim 28, Applicant argues Weiss does not teach or suggest a method for sequencing a target nucleic acid, that includes providing a set of nucleic acid fragments each containing a sequence that corresponds to a sequence of the target nucleic acid; hybridizing the set to an array of nucleic acid probes to form a target array of nucleic acids, where each probe includes a single-stranded portion including a variable region such that each member of the set hybridizes to a member of the array of probes, determining molecular weights of nucleic acids in the target array to identify hybridized probes, and based upon the hybridized probes, determining the sequence of the target nucleic acid. However, Weiss is not relied upon to teach any of the aforementioned limitations. Weiss is relied upon to teach using Beucage reagent to generate thiol moieties.

In response to Applicants' argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to

do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Weiss provides motivation with the statement, "By using the sulfurization reagent, each and every "O" group of the phosphodiester bond can be substituted with a sulfur group (see col. 19 lines 19-21)." One of skill in the art wanting to add sulfur groups to an oligonucleotide is clearly motivated to use Beucage reagent as taught by Weiss to achieve thiol modification of an oligonucleotide.

8. Regarding the 103 (a) rejection of claim 34, Applicants argue the combination of the teachings of Köster and Cantor does not result in the instantly claimed methods. Köster's teachings have been addressed above. Applicant argues Cantor does not teach or suggest a method for sequencing a target nucleic acid that includes providing a set of nucleic acid fragments each containing a sequence that that corresponds to a sequence of the target nucleic acid; hybridizing the set to an array of nucleic acid probes to form a target array of nucleic acids, where each probe includes a single-stranded portion including a variable region such that each member of the set hybridizes to a member of the array of probes; determining molecular weights of nucleic acids in the target array to identify hybridized probes', and based upon the hybridized probes, determining the sequence of the target nucleic acid.

In response to Applicants' arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Cantor is relied upon for teaching ligating the hybridized target nucleic acids to the probes. Further Cantor states, "Ligation of the target nucleic acid to the complementary probe increases fidelity of the hybridization (see col. 8 lines 8-9)." Inventions of both Cantor and Köster are directed to nucleic acid sequencing utilizing as a method step, hybridization. As

Cantor clearly states the advantage of ligating the hybridized target nucleic acid to its corresponding probe, one of skill would be motivated to utilize ligation with the hybridization method of Köster, and further as discussed above, Köster teaches determining molecular weights of nucleic acids in the target array to identify hybridized probes and subsequently determining the sequence of the target nucleic acid (see the abstract). Köster states, "The invention utilizes the Sanger sequencing strategy and assembles the sequence information by analysis of the nested fragments obtained base-specific chain-termination via their different molecular masses using mass spectrometry, as for example, MALDI or ES mass spectrometry. A further increase in throughput can be obtained by introducing mass-modifications in the oligonucleotide primer the chain-terminating nucleoside triphosphates and/or in the chain-elongating nucleoside triphosphates, as well as using integrated tag sequences which allow multiplexing by hybridization of tag specific probes with mass-differentiated molecular weights (see p. 9 lines 23-31).

9. With regard to the 103 (a) rejections of claims 71 and 72, Applicants argue the combination of the teachings of Köster and Cantor does not result in the instantly claimed methods. Köster's and Cantors teachings have been addressed above. Applicant argues Sanghvi does not teach or suggest the use of dimethoxytrityl or a derivative thereof as a selectively releasable bond by which to attach a probe to a solid support. Sanghvi does not teach or suggest using mass spectrometry, or using mass spectrometry for sequencing nucleic acids, or hybridizing a set of nucleic acid fragments containing a sequence that corresponds to a sequence of the target nucleic acid to an array of nucleic acid probes to form a target array of nucleic acids Sanghvi does not teach or suggest identifying hybridized probes by molecular weight, whereby the sequence of the target nucleic acid is determined.

In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800

F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Sanghvi is relied upon for teaching the selectively releasable bond is 4,4'-dimethoxytrityl or a derivative therof (see example 81 and col. 58 lines 3-32). Further as discussed above, Köster teaches determining molecular weights of nucleic acids in the target array to identify hybridized probes and subsequently determining the sequence of the target nucleic acid (see the abstract). Köster states, "The invention utilizes the Sanger sequencing strategy and assembles the sequence information by analysis of the nested fragments obtained base-specific chain-termination via their different molecular masses using mass spectrometry, as for example, MALDI or ES mass spectrometry. A further increase in throughput can be obtained by introducing mass-modifications in the oligonucleotide primer the chain-terminating nucleoside triphosphates and/or in the chain-elongating nucleoside triphosphates, as well as using integrated tag sequences which allow multiplexing by hybridization of tag specific probes with mass-differentiated molecular weights (see p. 9 lines 23-31). The combination of Köster and Sanghvi meet the limitations recited in claims 71 and 72.

10. With regard to the 103 (a) rejections of claims 38-39, 53, 55, 58-60, 63, 86, 88, 89-124, 128-144, applicant argues the combination of the teachings of Köster and Cantor does not result in the instantly claimed methods. Applicant continues to argue against the references individually. The teachings of Köster and Cantor have been addressed above. Applicants argue Cantor does not teach or suggest identifying hybridized probes in an array by determining the molecular weight of the hybridized probes. So even if Cantor teaches the probes, combining the teachings of Köster and Cantor do not teach or suggest every element of claim 1.

This is not persuasive because Cantor is relied upon for the variety of lengths of probes, the variable regions of probes and fragments of nucleic acids with greater than 104 different members each being between 10-1000 nucleotides in length. Inventions of both Cantor and Köster are directed to nucleic acid sequencing utilizing arrays of probes. As Cantor clearly states the advantage of utilizing

probes of varying length and variable regions, one of skill would be motivated to utilize these kinds of probes with the arrays and methods of Köster, and further as discussed above, Köster teaches determining molecular weights of nucleic acids in the target array to identify hybridized probes and subsequently determining the sequence of the target nucleic acid (see the abstract). Köster states, "The invention utilizes the Sanger sequencing strategy and assembles the sequence information by analysis of the nested fragments obtained base-specific chain-termination via their different molecular masses using mass spectrometry, as for example, MALDI or ES mass spectrometry. A further increase in throughput can be obtained by introducing mass-modifications in the oligonucleotide primer the chain-terminating nucleoside triphosphates and/or in the chain-elongating nucleoside triphosphates, as well as using integrated tag sequences which allow multiplexing by hybridization of tag specific probes with mass-differentiated molecular weights (see p. 9 lines 23-31).

Finally, Applicants argue the limitation in claim 124 of "a solid support comprising a matrix material that facilitates the volatilization of nucleic acids for mass spectrometry" is not suggested by the combination of Köster and Cantor. This is not persuasive because as outlined in the rejection Cantor teaches ceramics and membranes, as support matrices. Ceramic and membrane matrices are claimed by Applicants in dependent claim 136 as the matrix materials are structurally identical the matrices disclosed by Cantor necessarily meet the limitation "a matrix material that facilitates the volatilization of nucleic acids for mass spectrometry." Additionally, with respect to support matrices, Applicants argue the amended claims recite the limitation of a matrix chemical which facilitates volatilization and neither a ceramic matrix nor a membrane matrix is a chemical that facilitates volatilization. This argument is not persuasive because Köster teaches chemical matrices which meet the limitations recited in amended claims 75 and 124, 146 and 147. Specifically, Köster teaches at p. 38 lines 24-25, 3-hydroxypicolinic acid, sinapinic acid or dihydroxybenzoic acid.

Conclusion

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Heather G. Calamita whose telephone number is 571.272.2876 and whose e-mail address is heather.calamita@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route. The examiner can normally be reached on Monday through Thursday, 7:00 AM to 5:30 PM.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at 571.272.0782.

Papers related to this application may be faxed to Group 1637 via the PTO Fax Center using the fax number 571.273.8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to 571.272.0547.

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